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23 January 1991

Dear Charles,

Besides thanks for the encouragement (in the best sense: giving courage and insight) in getting us together, we're writing to ask your insight on ideas we've been discussing that involve Drosophila.

As we see it, the overall interest of our lab is on mechanisms that serve to focus the generation of genetic diversity. One class of these events, or one type of mechanism that may serve this end, is a possible relationship of transcription and mutagenesis. A scenario for focusing mutagenesis on transcribed genes might go like this: suppose that transcribed genes are more open, more exposed to the environment, more susceptible to chemical intercalation by environmental or endogenously produced mutagens. We have in mind experiments to explore this issue in bacteria (effects of transcription on mutatgenesis in the lacZ gene of E. coli), but we have also been led to consider Drosophila. Our reasoning, which was formulated in conversation with Mike Young, goes like this: Salivary gland puffs in drosophila might be more open and exposed. Salivary gland puffs are often associated with gene expression. Are salivary gland puffs preferentially penetrable by mutagens? For instance do mutagens that are DNA intercalators, like ethidium bromide, preferentially stain puffs?

Do you know if these type of experiments have been done? Are they within your ken? We respect that the world of Drosophila chromosomes and differentiated states of imprinting/packaging in them involves a lot of special knowledge. If the experiments have not been done and they deserve to be, would you be interested in collaboration?

The results with puffs would be of interest for their cytological results, but the puff DNA is a "dead end" i.e. it does not find its way back into the germ line. Do you know if genes that are expressed in the germ line of drosophila are particularly susceptible to heritable mutagenesis?

An approach most related to what we'll be attempting in bacteria would be to have a gene in drosophila that has controlled expression such that we'd be able to modulate expression in the germ line. The question that we want to ask is if the gene is expressed in the germ line is it going to be more likely to give rise to a heritable mutant allele? What would be the best choice of controllable promoters and what would be the best choice of target genes? We imagine that selection would be highly desirable, rather than a screening approach, in order to achieve high sensitivity. What is the dynamic range of mutagensis which is quantifiable in drosophila?

Thanks for your indulgence of our questions. We're pummeling you with them because of a hunch that your the best person to help!

Sincerely,

Joshua Lederberg

David Thaler

LAIRD